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EXAMINER	
MACFARLANE, STACEY NEE	
ART UNIT	PAPER NUMBER
1649	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/647,654	INGHAM ET AL.	
	Examiner	Art Unit	
	STACEY MACFARLANE	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,11-13,23-26 and 49-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,11-13,23-26 and 49-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/5/2007; 3/3/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 5, 2007 has been entered.

Response to Amendment

2. Claims 1, 2, 5, 6, 12-13, 23-26 and 49-56 have been amended, and claims 57-81 newly added, as requested in the amendment filed on November 5, 2007. Following the amendment, claims 1-3, 5, 6, 11-13, 23-26 and 49-81 are pending in the instant application.

3. Applicant's arguments filed with the RCE on November 5, 2007 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Election/Restrictions

4. Applicant's election with traverse of Group IV, drawn to methods comprising contacting cells with the polypeptide of SEQ ID NO: 13, in the reply filed on March 3, 2008 is acknowledged. The traversal is on the ground(s) that claims are Markush claims that all recite particular species of Sonic hedgehop polypeptides and that the

restriction requirement should be deemed an election of species. This is not found persuasive because, as indicated in section 4 of the Requirement for Restriction mailed January 31, 2008, the methods of Groups I-IV are materially distinct, each requiring a structurally distinct polypeptide with a unique sequence identifier. Each sequence has a distinct utility and because these products are structurally distinct molecules, the search of each of these products is not coextensive. In cases as this one where descriptive sequence information is provided, the sequences are individually searched in appropriate databases. Sequence searches require an extensive analysis of the art retrieved and require an in-depth analysis of technical literature that presents a serious burden upon the Examiner. There is a search burden also within the non-patent literature as well as in electronic databases. Furthermore, section 803.02 of the MPEP states, "a Markush-type claim may include independent and distinct inventions. This is true where two or more of the members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the claim obvious under 35 U.S.C. 103 with respect to the other member(s)". A prior art reference that teaches the method comprising, for example, the sequence of SEQ ID NO: 13 would not necessarily anticipate or render obvious under 103 the same method comprising SEQ ID NO: 8. As stated in section 4 of the Requirement for Restriction (*Id*), the courts have maintained the precedent that even a single amino acid change does not constitute an obvious variant upon a polypeptide as that single amino acid change may vastly affect the physiological properties of the protein. Thus, because

these methods are materially distinct, are not obvious variants, and present a serious search burden, they are restricted under 35 U.S.C. 121.

The requirement is still deemed proper and is therefore made FINAL.

5. Claims 1-3, 5, 6, 11-13, 23-26 and 49-81, in so far as they are drawn to SEQ ID NO: 13, will be examined upon their merits in the instant Office Action.

Claim Objections

6. Claims 1, 2, 6, 23, 25, 26, 49, 50, 53, 63 and 64 are objected to for reciting non-elected subject matter (namely, SEQ ID NO: 8, SEQ ID NO: 11 and SEQ ID NO: 12). Appropriate correction is required.

Priority

7. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120, 121, or 365(c) as follows: The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See Transco Products, Inc. v. Performance Contracting, Inc., 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 08/176,427, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The application does not provide support for the human sequence Sonic hedgehog (*Shh*), therefore it does not support the instant claims drawn to a method comprising contacting cells with SEQ ID NO: 13, human *Shh*. Therefore, the examined subject matter of claims 1-3, 5, 6, 11-13, 23-26 and 49-81 will only be afforded the benefit to parent application 08/356,060 (now US Patent 5,844,079), filed December 14, 1994, for which there is enabling support for the human amino acid sequence of SEQ ID NO: 13.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-3, 11-13, 23-24, and 49-81 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2 and 23 recite a method comprising contacting a cell with a Sonic hedgehog polypeptide (Shh) comprising “an amino acid sequence designated in (instantly- elected) SEQ ID NO: 13, or an N-terminal fragment thereof having a

molecular weight of approximately 19 kDa". Claims 11-13, 23-24, and 49-63 are dependent claims that and do not further limit the "amino acid sequence designated in (instantly- elected) SEQ ID NO: 13, or an N-terminal fragment thereof having a molecular weight of approximately 19 kDa", and are therefore included in the rejection. The claims broadly read upon any amino acid sequence, read as any two or more amino acids, anywhere within the sequence of SEQ ID NO: 13, or any N-terminal fragment thereof with a MW of 19 kDa. The claims do not require that the "amino acid sequence" possess any particular conserved structure, but require that these peptide sequences "bind a naturally occurring hedgehog receptor and promote hedgehog signaling", "mimic the effects of a naturally-occurring hedgehog protein" or provide "a means for promoting hedgehog signaling". Since there is no conserved structure there is likewise no disclosed structure to function correlation for the sequence of the claims. Thus, the claims are drawn to a genus of molecules that is defined only by function and the instant specification fails to describe the entire genus of molecules that are encompassed by these claims.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant has possession of and what Applicant is claiming. From the specification, it is clear that Applicant is in possession of specific examples of Shh polypeptides that bind the hedgehog receptor and promote hedgehog signaling, namely, the full length amino acid sequence of human hedgehog consisting of SEQ ID NO: 13, and the "auto-proteolytic fragment" as explicitly defined within the specification as

"about Cys-198 through Ala-475 of the human Shh protein" (line 25, page 4 of specification). The claims, however, encompass method of administration of an amino acid sequence designated in SEQ ID NO:13, and N-terminal fragments weighing approximately 19 kDa. Thus, the claims are not limited to specific molecules with known structure. The claims merely require the claimed methods employ molecules that serve to bind a naturally occurring hedgehog receptor, promote hedgehog signaling and mimic the effects of a naturally-occurring hedgehog protein.

Furthermore, claims 49 and 52 encompass a method comprising contacting a cell with "an amino acid sequence encoded by a nucleic acid that hybridizes … to a nucleic acid sequence of SEQ ID NO: 6", which is the encoding sequence for the instantly-elected polypeptide of SEQ ID NO: 13. Due to both the degeneracy of the genetic code and issues of sensitivity and specificity within hybridization techniques, these claims read upon variants of the two or more amino acids designated in SEQ ID NO: 13, as claimed in Claims 1, 2 and 23. The following reference demonstrates that even a single change at the amino acid level can dramatically alter protein function (Guo et al. *PNAS, USA*, 101(25): 9205-9210, June 22, 2004). Furthermore, there is little predictability within predictive protein function from nucleic acid sequence (Bowie et al., Science 247:1306-1310, March 1990).

Claims 66-81 are even more broadly drawn to a method comprising contacting a cell with "a means for" promoting hedgehog signaling and the specification has neither explicitly defined those materials that are a "means for promoting hedgehog signaling"

nor has it adequately described the structure or materials that correspond to a "means for".

In order to provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In the instant case, the only requisite factor present in the claim is a recitation of activity and there is not even identification of any particular portion of the structure that must be conserved for said activity. As stated above, it is not even clear what molecules possess said activities except the full length amino acid sequence consisting of SEQ ID NO: 13 and the proteolytic N-terminal fragment consisting of about Cys-198 through Ala-475 of SEQ ID NO: 13. The specification does not provide a partial structure of any other fragment or sequence within SEQ ID NO: 13 that fulfills the requirement of the claimed activity, and thus, the disclosure fails to provide a representative number of species for the recited genus. Therefore, without adequate structural description or structure-to-function correlation, one of ordinary skill in the art would not recognize those fragments or variants that are encompassed by the claims and fulfill the requisite functions of binding a naturally occurring hedgehog receptor and promote hedgehog signaling, mimicking the effects of a naturally-occurring hedgehog protein or providing a means for promoting hedgehog signaling. Accordingly,

in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, the court clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the molecular structure of the encompassed genus of amino acid sequences, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of identifying activity. Adequate written description requires more than a mere recitation of activity as part of the invention and a reference to a potential method of isolating or screening. The compound itself is required. See *Fiers v Revel*, 25 USPQ2d 1601 at 1601 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification only provided for the bovine sequence.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

10. Claims 1-3, 5, 6, 11-13, 23-26 and 49-81 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of promoting growth, differentiation and/or survival of embryonic neural tube or neural plate cells by administering a Shh polypeptide consisting of SEQ ID NO: 13 or the N-terminal proteolytic fragment thereof (as defined by line 25, page 4 of the specification), does not reasonably provide enablement for administering any other amino acid sequence designated within SEQ ID NO: 13, nor for the administration of portions of the polypeptides other than that of the N-terminal autoproteolytic portion, nor does the specification provide enablement for promoting growth, differentiation and/or survival of neuronal cells other than embryonic cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1, 2, 23, 49, 52 and 66-81 broadly encompass methods comprising contacting a dopaminergic cell, a mammalian neuronal cell or any cell (as in claim 23) with any amino acid sequence designated within SEQ ID NO: 13, any fragment or variant thereof, or any means for promoting hedgehog signaling, wherein the method results in the promotion of proliferation, differentiation and/or survival of a neuronal cell, or results in the induction of any cell to differentiate to a dopaminergic or motor neuron.

The invention is based on working examples 9 and 10 within the specification. Example 9 demonstrates that contact of embryonic neural tube cells with mouse Shh protein, or the N-terminal proteolytic fragment thereof, induces differentiation of the embryonic explant tissue to motorneuron phenotype. Example 10 demonstrates that contacting the cells of the intermediate third of the embryonic neural plate leads to the induction to differentiate to a dopaminergic phenotype. However, the instant specification is not found to be enabled for the method as claimed, for the following reasons. The instant specification provides neither enough guidance for such method of determination, nor working examples, which would show that the claimed method was successfully achieved with any other amino acid sequence, or means for promoting hedgehog signaling, encompassed by the claims. Absent such guidance, one of ordinary skill in the art would require undue experimentation to discover how to practice Applicant's invention to the full scope as claimed.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The nature of the invention relates to methods for promoting cellular differentiation, proliferation or survival comprising contacting cells with a Sonic hedgehog protein.

The state of the art at the time of filing recognized that the hedgehog family of polypeptides mediates Drosophila and vertebrate development (Fietz et al., 1994 cited as reference “BR” on the IDS dated June 14, 2004). Specifically, hedgehog polypeptides induce the differentiation of the zone of polarizing activity (ZPA) which controls embryonic limb formation (Riddle et al., 1993 cited as reference “ES” on the IDS dated June 14, 2004) and notochord and floor plate differentiation into the central nervous system (Echelard et al., 1993 cited as reference “BK” on the IDS dated June 14, 2004).

With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the scope of enablement, the claims are analyzed with respect to the teachings of the specification and are to be given their broadest reasonable interpretation that is consistent with the specification. See MPEP 2111 [R-1], which states: "During patent examination, the pending claims must be "given *>their< broadest reasonable interpretation consistent with the specification." In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). Applicant always has the opportunity to amend the claims during prosecution, and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550- 51 (CCPA 1969)".

As such, the broadest reasonable interpretation of the claimed method is that it allows for promoting proliferation, differentiation and/or survival of a cell comprising

contacting the cell with any means for promoting hedgehog signaling. Thus, the claims encompass an unreasonable number of methods as applied to any cell and comprising any material that promotes hedgehog signaling. A skilled artisan would not know how to perform these methods to the full scope of the claims. As stated above in section 9, there is not even adequate description of the structures or materials that are encompassed by the full scope of the claimed method. Furthermore, as opposed to the what is claimed, what is disclosed about the claimed method is narrow: The working examples provide guidance as to how to contact embryonic neural tube cells with mouse Shh protein, or the N-terminal proteolytic fragment thereof, to induce differentiation of the embryonic explant tissue into a motorneuron phenotype, or how to contact the cells of the intermediate third of the embryonic neural plate leads with human or mouse hedgehog protein in order to induce differentiation to a dopaminergic phenotype. Therefore, the disclosure provides no guidance as to how to use the invention to the full extent of the scope claimed.

While the skill level in the art is high, the level of predictability is low. As stated above, The state of the art at the time of filing recognized that the hedgehog family of polypeptides induces the differentiation of the ZPA, notochord and floor plate, which are essential stages along the pathway of embryonic motorneuron and neuronal phenotypes. Since the cells of these regions give rise to all neurons, then the induction of a dopaminergic neuronal fate is induced by hedgehog as well and Applicant's data demonstrating that, upon contact with hedgehog, embryonic cells of from these regions are induced to proliferate, differentiate and/or survive, confirms this state of the art.

Applicant, however, has not demonstrated that contact with hedgehog, an N-terminal portion thereof, or a "means for" hedgehog signaling induces the proliferation, differentiation, or survival of any cell, as broadly claimed.

The standard of an enabling disclosure is not the ability to make and test if the invention works but one of the ability to make and use with a reasonable expectation of success. A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of Genentech, Inc, v. Novo Nordisk, 42 USPQ 2d 1001, (CAFC 1997), the court held that:

> "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because one of ordinary skill in the art cannot follow the guidance presented therein and practice the claimed method to the full extent of the scope, without first making a substantial inventive contribution. In order to practice the method a skilled artisan would have to first identify specific N-terminal fragments of hedgehog, or variant polypeptides comprising an amino acid sequence encoded by a nucleic acid that hybridizes to SEQ ID NO: 6, or materials that provide a "means for promoting hedgehog signaling", and then, demonstrate that upon contact with said compounds, dopaminergic neurons, motorneurons, neural stem cells, or any

cell would be induced to proliferate, differentiate and/or survive. Such experimentation goes beyond the realm of what would be considered within the art as routine experimentation, and constitutes undue experimentation on the part of the practitioner. Therefore, the claims are rejected for lack of enabling support.

Conclusion

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STACEY MACFARLANE whose telephone number is (571)270-3057. The examiner can normally be reached on M, W and ALT F 7 am to 3:30, T & R 5:30 -5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stacey MacFarlane
Examiner
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/John D. Ulm/
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